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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,963	RUBINSTEIN ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32 and 34* is/are pending in the application.

4a) Of the above claim(s) *4,16 and 20-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-15,17-19 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 21 June 2005 as the U.S. national stage of international application PCT/IL03/00815 filed 9 October 2003, which claims benefit of Israeli application 152232 filed 10 October 2002. The preliminary amendments filed 11 April 2005 and 27 August 2007 have been entered. Claims 1-34 were originally filed. Claim 33 was cancelled and claims 5, 7, 12, 15-17, 22, 26, 28, 30 and 32 were amended in the 11 April preliminary amendment. Claims 1 and 34 were amended in the 27 August preliminary amendment. Claims 1-32 and 34 are pending.

Election/Restrictions

Applicant's election with traverse of Group I and the species SEQ ID NO: 2, IFN-β and CHO cell in the reply filed on 27 August 2007 is acknowledged. The traversal is on the ground(s) that the claims have been amended to recite the generic function "human IL-18BP promoter activity" and therefore share a common special technical feature. This is not found persuasive because nucleic acids having IL-18BP promoter activity were known in the art prior to the effective filing date of the instant application (see *infra*). Therefore, the claims still lack a unifying special technical feature.

The requirement is still deemed proper and is therefore made FINAL.

Claims 16 and 22-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and claims 4, 20 and 21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected, there being

no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the 27 August reply.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-3 and 5-9 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims, as written, do not sufficiently distinguish over the human IL-18BP gene as it is found in nature because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. With regard to claim 9, which recites that the gene encodes a heterologous protein, it is noted that the claim does not specify the relative standard for determining that an encoded protein is "heterologous". As all proteins are heterologous to something, the naturally occurring IL-18BP gene reads on the DNA sequence of claim 9[1]. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" as taught in the working examples of the specification. See MPEP 2105.

Claims 13 and 14 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are directed to a host cell comprising a

[1] It would be remedial to amend the claim to recite that the encoded protein is heterologous to the IL-18BP gene if that is what is intended.

vector according comprising the IL-18BP promoter of claim 1. The specification contemplates using vectors comprising the IL-18BP promoter in methods of gene therapy which include introducing the vector into cells in a human. (See especially the discussion bridging pages 19-20 of the specification.) Given these teachings, the broadest reasonable interpretation of the claims clearly encompasses a cell that might be present or is intended to be present in a human being, said cell becoming integrated into the human being and therefore being an inseparable part of the human itself. The scope of the claim, therefore, encompasses a human being, which is non-statutory subject matter. As such, the recitation of the limitation "non-human" or "isolated" would be remedial. See 1077 O.G. 24, April 21, 1987.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 34 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior

art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The claim is directed to a pharmaceutical composition comprising a therapeutically effective amount of a DNA sequence encoding the human IL-18BP functional promoter. As the claim is drawn to a pharmaceutical composition, the claimed composition is construed as intended for pharmaceutical use and enablement for the claimed invention is evaluated based on that intended use[2]. Furthermore, as the claim requires that the composition comprise a therapeutically effective amount of the DNA sequence, it is incumbent upon the disclosure to teach the skilled artisan how to make a composition comprising a therapeutically effective amount of the vector.

With regard to the scope of the claims, it is noted that the IL-18BP promoter of the claims does not itself have any therapeutic properties. Therefore, the therapeutic activity of the claimed nucleic acid is dependent upon the properties of the nucleic acid expressed from the promoter, which is undefined in the claims. As the enabling specification must teach those skilled in the art to make and use the full scope of the claimed invention without undue experimentation[3], it is also incumbent upon the specification to teach the manner and process of making the claimed

[2] MPEP 2164.01(c) states: "When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991)."

[3] "Although not explicitly stated in section 112, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without "undue experimentation." *Vaeck*, 947 F.2d at 495, 20 USPQ2d at 1444; *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404; *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

invention commensurate with the broad scope of the claims.

State of the prior art and level of predictability in the art: The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability.

The physiological art is recognized as unpredictable. (MPEP 2164.03.) In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

At the time of filing, *in vivo* gene therapy utilizing the administration of recombinant nucleic acids, regardless of the mode of delivery (*e.g.*, adenovirus, retrovirus, liposome), was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) *Nature* Volume 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, "difficulties in getting genes

transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) *Science*, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck *et al.* (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Edition, Chapter 5, McGraw-Hill, NY, explains, "the delivery of exogenous DNA and its processing by target cells require the introduction of new pharmakokinetic paradigms beyond those that describe the conventional medicines in use today". Eck *et al.* teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (see Eck *et al.* bridging pages 81-82).

Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of

therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, "...the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross *et al.* Human gene Therapy, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph).

In an article published shortly before the effective filing date of the instant application, Rubanyi (2001) *Mol. Aspects Med.* 22:113-142 teaches that the problems described above remained unsolved at the time the instant application was filed. Rubanyi states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see especially "**3. Technical hurdles to be overcome in the future**", beginning on page 116 and continued through page 125).

Beyond the technical barriers common to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. Rubanyi teaches, "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic" (bridging pages 131-132).

Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing any putatively therapeutic gene using any given expression construct was highly unpredictable.

Amount of direction provided by the inventor and existence of working examples: The teachings of the instant disclosure with regard to therapeutic application of the claimed composition are speculative and prophetic. Pages 19-23 the specification provide generic teachings regarding possible vectors that might be used in the composition and contemplates targeting hematopoietic stem cells for *ex vivo* delivery of genes. The application particularly contemplates suppression of HIV-1 replication by expression of anti-HIV-1 genes, but provides no specific guidance as to how to use a composition comprising an anti-HIV-1 gene or how to prepare a therapeutically effective amount of the composition. The working examples of the application demonstrate expression of a heterologous reporter gene *in vitro*, but there is no evidence of therapeutic effect obtained using any construct reduced to practice in the application.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, one of ordinary skill would not be able to make and use the claimed pharmaceutical composition without undue experimentation. The pharmaceutical composition of the claims encompasses a highly heterogeneous genus of nucleic acids defined only by the presence of an IL-18BP promoter (or fragments of derivatives thereof). However, the pharmaceutical properties of the composition would vary greatly depending upon the nature of the nucleic acid operatively linked to the IL-18BP promoter. As the field of gene therapy is highly unpredictable and the disclosure provides no specific guidance as to how to obtain a therapeutic effect with any embodiment within the scope of the claim, one of skill in the art seeking to make and use the claimed pharmaceutical composition according to the recited intended use would have to engage in undue experimentation to identify embodiments within the claim scope that could be used

therapeutically and then empirically determine a therapeutically effective amount of each embodiment within the claim scope.

Given the unpredictable nature of the art, the tremendous breadth of the claim and the absence of specific guidance in the disclosure as to how to use the claimed pharmaceutical composition or how to prepare a therapeutically effective amount of any DNA sequence within the scope of the claim, making and using the claimed invention would require undue experimentation. Therefore, the claimed invention is properly rejected under 35 USC § 112, first paragraph, as lacking enablement for the full scope of the claimed invention.

Claim Construction

Office personnel are to give claims their broadest reasonable interpretation in light of the supporting disclosure. *In re Morris*, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997).

The instant claim 1 is directed to a DNA sequence encoding the functional IL-18BP promoter encoded by SEQ ID NO: 1, or a functional human IL-18BP promoter activity containing fragment or a functional human IL-18BP promoter activity containing derivative thereof wherein the 3' end of said DNA sequence or fragment thereof comprises one to 51 nucleotides from the 5' end of SEQ ID NO: 5. It is first noted that the claim is construed as directed to a nucleic acid or DNA molecule comprising a sequence encoding the functional IL-18BP promoter (or fragment or derivative)[4]. The recitation "wherein the 3' end of said DNA

[4] A DNA sequence *per se* is a representation of a DNA molecule. As such, claiming a DNA sequence is akin to claiming a drawing or paragraph describing a machine. Applicant is urged to amend the claim to clearly indicate that the claimed invention is a nucleic acid or DNA molecule, as a DNA sequence *per se* is not patentable subject matter.

sequence or fragment thereof comprises one to 51 nucleotides from the 5' end of SEQ ID NO: 5", according to its broadest reasonable scope, requires only that the portion of the claimed nucleic acid encoding the functional IL-18BP terminate with a cytosine (i.e., the 5' terminal nucleotide of SEQ ID NO: 5) at its 3' end. Furthermore, as the application provides no specific definition of what constitutes the 3' end of a DNA sequence encoding a functional IL-18BP or fragment thereof, the claim is understood to read on any nucleic acid comprising a DNA sequence encoding an IL-18 promoter activity containing fragment or derivative, wherein the nucleic acid also comprises a cytosine residue downstream of the promoter functional elements which can be arbitrarily identified as the 3' end of the sequence encoding the promoter. It is noted that the arbitrary designation of the 3' end is supported by dependent claim 3, which requires that the fragment comprise SEQ ID NO: 2. The 3' end of SEQ ID NO: 2 consists of the sequence "T-T", which does not appear anywhere in SEQ ID NO: 5. Therefore, the claims must read on molecules wherein the 5' cytosine of SEQ ID NO: 5 is arbitrarily upstream or downstream of the explicitly recited 3' end of the sequence.

With regard to fragments and derivatives comprising IL-18BP promoter activity, Applicant cites a passage at page 10, lines 9-24 in support of the recitation IL-18BP promoter activity in the remarks filed 27 August 2007. According to the cited passage, IL-18BP promoter activity broadly encompasses the capacity to direct gene expression. (Page 10, lines 12-13.) As the claims place no limit on the size of the fragment or the extent of derivatization, the fragments and derivatives of the claims are broadly construed as covering any nucleic acid having the capacity to direct gene expression (i.e., any promoter). In the interest of brevity, only the most

relevant art is cited herein. However, any nucleic acid comprising a promoter could be cited against the claims as written.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 and 5-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Entrez Nucleotide Database entry for Accession No. AF110798, http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=nuccore&id=4324923, published 3 March 1999, downloaded 29 October 2007 (hereinafter, the AF110798 sequence).

The AF110798 sequence discloses a nucleic acid comprising nucleotides 490-1272 of the instant SEQ ID NO: 1 (i.e., the sequence from 1 to 789 of the AF110798 sequence) and the entirety of the instant SEQ ID NO: 2 (i.e., the sequence from 150 to 783). According to the description of the IL-18BP gene presented in the instant application (see, e.g., the final paragraph on page 9), this region would comprise at least the minimal promoter (SEQ ID NO: 3 is found at bases 662-782 of the AF110798 sequence), the GAS sequence at –24 to –32 relative to the transcriptional start site at 784 of the AF110798 sequence, the IRF-E sequence at –57 to –69 relative to the transcriptional start site and the C/EBPβ response elements at –309 to –322 and –621 to -634. If one arbitrarily identifies the "C" residue at base 784 as the 3' end of the DNA

sequence encoding the promoter, the nucleic acid disclosed in the AF110798 sequence comprises all of the elements of the nucleic acid claimed in the instant claim 1.

In addition, the AP1 sites present in the native IL-18BP nucleic acid are omitted from the AF110798 sequence which reads on a nucleic acid comprising a mutation (i.e., deletion) of the AP1 site according to claim 2 and the nucleic acid comprises SEQ ID NO: 2 according to claim 3 (*Id.*). The AF110798 sequence comprises the entire IL-18BP nucleic acid coding sequence and therefore comprises the intron of claims 5 and 6 and the operatively linked gene of claims 7 and 8. Finally, as described above, claim 9 does not specify the relative standard for determining that an encoded protein is "heterologous". As all proteins are heterologous to something, the naturally occurring IL-18BP gene also reads on the DNA sequence of claim 9.

Thus, the AF110798 sequence discloses a nucleic acid comprising all of the elements of the nucleic acid claimed in the instant application. Therefore, the claims are anticipated by the AF110798 sequence.

Claims 1-3, 5-9, 12 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Entrez Nucleotide Database entry for Accession No. AP000719, http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=nuccore&id=13094220, sequence published prior to 23 July 2002 (see the attached revision history which shows no sequence modifications made after 23 July 2002), downloaded 28 October 2007 (hereinafter, the AP000719 sequence) as evidenced by Osoegawa et al. (2001) Genome Res. 11:483-496.

The AP000719 sequence discloses a nucleic acid comprising the entirety of the instant SEQ ID NO: 1 and SEQ ID NO: 2 (i.e., the sequence from 150907-152178). According to the

description of the IL-18BP gene presented in the instant application (see, e.g., the final paragraph on page 9) this region of the AP000719 sequence would comprise all of the regulatory elements of the instant IL-18BP promoter. If one arbitrarily identifies the "C" residue at base 152179 as the 3' end of the DNA sequence encoding the promoter, the nucleic acid disclosed in the AF110798 sequence comprises all of the elements of the nucleic acid claimed in the instant claim 1.

With regard to claim 2, the AP1 sites identified in the instant application would be present in the AP000719 sequence. However, the AP000719 sequence is viewed as reading on the claim because the application does not specify any structural or functional properties of a "mutant AP1 site" (e.g., the AP1 site comprises sequence A and does not bind AP1). As all nucleic acid sequences are the product of mutation and selection (natural or otherwise) the limitation "mutant AP1 site" reads on any sequence that is not an AP1 site or any AP1 sequence produced by a process of mutation (i.e., all AP1 sites).

The AP000719 sequence comprises the entire IL-18BP nucleic acid coding sequence and therefore comprises the intron of claims 5 and 6 and the operatively linked gene of claims 7 and 8. As described above, claim 9 does not specify the relative standard for determining that an encoded protein is "heterologous". As all proteins are heterologous to something, the naturally occurring IL-18BP gene also reads on the DNA sequence of claim 9.

Finally, the AP000719 sequence entry teaches that the sequence is comprised in an RP11 clone (a.k.a., RPC-11; see under "DEFINITION"). Osoegawa et al. teaches that RPC-11 is a BAC library. (See especially page 492, second sentence of the "DISCUSSION".) In view of the fact that nucleic acids in BAC libraries are comprised within vectors and propagated in bacteria,

the vector of claim 12 and host cell of claim 13 are inherent to the teaching of the nucleic acid comprised in an RP11 clone as disclosed in the AP000719 sequence.

Thus, the AP000719 sequence as evidenced by Osoegawa et al. comprises all of the elements of the nucleic acid claimed in the instant application. Therefore, the claims are anticipated by the AP000719 sequence.

Claims 1-3, 7, 9, 10 and 12 rejected under 35 U.S.C. 102(b) as being anticipated by Hurgin et al. (2001) *Journal of Interferon and Cytokine Research* 24:S. 73 (made of record in the IDS filed 11 April 2005).

Hurgin et al. teaches a 2 kb genomic sequence upstream of the human IL-18BP gene contains a promoter and enhancer element as determined by luciferase reporter vectors. Absent evidence to the contrary, one of skill in the art would conclude that the promoter sequences recited in the instant claims are inherent to the reporter vectors of Hurgin et al. in view of the fact that Hurgin et al. is characterizing the promoter region of the human IL-18BP gene (the sequence of which was known in the art at the time the instant application was filed (see, the AF110798 and AP000719 sequences *supra*). Therefore, the luciferase reporter constructs of Hurgin et al. anticipate the nucleic acid of claims 1-3, 7, 9 and 10 and the vector of claim 12.

Claims 1, 2, 7, 9, 11-14, 17-19 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Oda et al. (1993) EP 0 546 333 A1.

Independent claim 1 is directed to a DNA sequence encoding...a functional human IL-18BP promoter activity containing fragment or a functional IL-18BP promoter activity containing derivative...wherein the 3' end of said...fragment...comprises one...nucleotide[]

from the 5' end of SEQ ID NO: 5. The application discloses that the sequence at –24 to –32 relative to the transcriptional start site of the IL-18BP promoter (i.e., the sequence 'ttcccagaa') has the function of a gamma-activated sequence (GAS). As the application provides no limiting definition of an IL-18BP promoter activity-containing fragment or derivative, the sequence 'ttcccagaa', which has the function of a GAS (i.e., an activity contained by the IL-18BP promoter), is reasonably construed as within the scope of the claims.

Oda et al. teaches a promoter sequence that comprises the sequence 'ttcccagaa' followed by a 'c' (see especially positions –1796 to –1805 of the sequence set forth in Figure 3), which promoter sequence has the capacity to direct expression of a nucleic acid operably linked thereto (see especially the working examples, which teach the construction of vectors comprising CAT and interferon γ genes operably linked to the promoter sequence set forth in Figure 3). The promoter of Oda et al. meets the limitations of independent claim 1 according to the broadest reasonable interpretation thereof. Furthermore, the compositions comprising constructs comprising the human interferon γ gene described in Example 2 is the same as the pharmaceutical composition of independent claim 34.

In addition, the limitations of the dependent claims are also found in the teachings of Oda et al. The promoter of Oda et al. does not comprise an AP1 site (i.e., the same as a deletion of an AP1 site) according to the instant claim 2; the constructs of Oda et al. comprise genes operably linked to the promoter that encode heterologous proteins according to the instant claims 7 and 9; and the working examples teach expression of the heterologous proteins in mammalian cells according to the limitations of claims 12-14. Oda et al. further contemplates the use of a retroviral vector according to the instant claim 17. Furthermore, as the application provides no

definition of what constitutes the minimum "portion of a virus genome" according to the requirements of claim 19, the retrovirus of Oda et al. would comprise portions of an AAV genome (e.g., nucleotides) sufficient to meet the requirements of claim 19.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hurgin et al. (*supra*), as applied to claims 1 and 12 herein above, in view of Guan et al. (1995) *J. Biol. Chem.* 270:21958-21965.

Claims 13-15 are directed to a host cell comprising the vector according to claim 12 (claim 13), wherein the host cell is a mammalian cell (claim 14) or a CHO cell (claim 15). The limitations of claims 1 and 12 and the teachings Hurgin et al. are described herein above. Although Hurgin et al. teaches that the promoter region of the human IL-18BP gene was characterized using a luciferase reporter vector, Hurgin et al. does not specify the cells used in the characterization method. Guan et al. teaches a method of characterizing a different human gene promoter using a luciferase reporter vector and teaches that CHO cells are a suitable host for such an assay. (See especially the paragraph bridging the left and right columns on page 21959, the paragraph bridging the left and right columns on page 21961, the first full paragraph in the right column on page 21961, Figure 5 and the caption thereto.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a CHO cell line to test the luciferase reporter vectors taught by Hurgin et al. In *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found in the prior art," (*Id.* At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on it precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." (*Id.* At 1395.) In the instant case, Hurgin et al. teaches the characterization of the human IL-18BP promoter using

luciferase reporter plasmids and Guan et al. teaches that it was known in the art long before the instant application was filed that CHO cells are suitable host cells for testing luciferase reporter vectors. The only difference between the claimed invention and the prior art is the combination of elements known in the art. However, one of ordinary skill in the art could have combined the elements as claimed by known methods and, in that combination, each element would merely have performed the same function it did separately. As CHO cells were routinely used in the art for such assays, the results of combining the prior art elements would have been predictable to one of skill in the art at the time the invention was made.

Thus, all of the elements of claims were known to one of ordinary skill in the art at the time the invention was made and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art at the time of invention. Therefore, the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made.

Claims 11 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oda et al. *supra*), as applied to claims 9 and 17 herein above, in view of McCormick et al. (1990) US Patent No. 4,966,843.

Claims 11 and 18 are directed to the nucleic acid of claim 9 and the recombinant virus vector of claim 17, respectively, wherein the nucleic acid or vector further comprises a gene encoding interferon beta. As described above, the teachings of Oda et al. anticipate the limitations of claims 9 and 17. Oda et al. fails to teach an embodiment wherein the nucleic acid

or vector comprises interferon beta. However, Oda et al. teaches, "any structural gene which may be expressed in mammalian cells may be employed" (column 6, lines 28-30) and reduces to practice an embodiment wherein the structural gene encodes interferon gamma.

McCormick et al. teaches methods directed to the *in vitro* expression of polypeptides similar to those of Oda et al. and demonstrates *in vitro* expression of IFN-β. (See especially columns 15-20.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include IFN-β among the proteins expressed using the vector system of Oda et al.. In *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found in the prior art," (*Id.* At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on it precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." (*Id.* At 1395.) In the instant case, Oda et al. teaches any structural gene which may be expressed in mammalian cells may be employed in the expression system described therein (*Id.*) and reduces to practice an embodiment wherein the structural gene encodes interferon gamma, and McCormick et al. teaches that interferon beta was among the proteins expressed *in vitro* mammalian expression systems. The only difference between the claimed invention and the prior art is the combination of elements known in the art. However, one of ordinary skill in the art could have combined the elements as claimed by known methods and, in that combination, each element would merely have performed the same function it did separately. As Oda et al. demonstrates that proteins such

as interferon gamma can be successfully expressed using the nucleic acid and *in vitro* expression system disclosed therein and McCormick et al. demonstrates that interferon beta can be successfully expressed in mammalian cells *in vitro* the results of combining the prior art elements would have been predictable to one of skill in the art at the time the invention was made.

Thus, all of the elements of claims were known to one of ordinary skill in the art at the time the invention was made and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art at the time of invention. Therefore, the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel M Sullivan/
Primary Examiner
Art Unit 1636